May 13, 2019

Effectiveness of transmitted drug resistance testing before initiation of antiretroviral therapy in HIV-positive individuals

The HIV-CAUSAL Collaboration*

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Number of words: abstract (248), manuscript (3035)

Number of tables (3), number of figures (1), number of Appendices (6)

Key words: transmitted drug resistance; antiretroviral treatment; genotypic testing;

Funding: This work was supported by NIH grant R37 AI102634

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Conflicts of Interest

HF Günthard has received unrestricted research grants from Gilead Sciences and Roche; fees for data and safety monitoring board membership from Merck; consulting/advisory board membership fees from Gilead Sciences, Merck, Sandoz and Mepha. AN Phillips has received funding the Bill & Melinda Gates Foundation; Heiner C. Bucher has received in the 36 months prior to the submission of this manuscript grants, support for travelling, consultancy fees and honorarium from Gilead, BMS, Viiv Healthcare and Roche that were not related to this project. He serves as the president of the association contre le HIV et autres infections transmissibles. In this function he has received support for the Swiss HIV Cohort Study from ViiV Healthcare, Gilead, BMS, MSD and AbbvieC Sabin received funding from Gilead Sciences, ViiV Healthcare and Janssen-Cilag for the membership of Data Safety and Monitoring Boards, Advisory Boards, Speaker Panels and for the preparation of educational materials; ; A van Sighem reports grants from Dutch Ministry of Health, Welfare and Sport, during the conduct of the study; grants from European Centre for Disease Prevention and Control, outside the submitted work. P Reiss through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co, and ViiV Healthcare; he has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, Merck & Co, Teva pharmaceutical industries, and on a data safety monitoring committee for Janssen Pharmaceuticals Inc for which his institution has received remuneration. K Porter received funding from ViiV Healthcare and Merck for advisory board memberships and speaker panels. No other conflict of interest to report.

Author contribution statement

Conception: Sara Lodi, Miguel Hernan; Study design: Sara Lodi, Miguel Hernan; Acquisition of data: Huldrych F. Günthard, John Gill, Andrew N. Phillips, David Dunn, Quang Vu, Reed Siemieniuk, Federico Garcia, Roger Logan, Sophie Jose, Heiner C. Bucher, Alexandra U. Scherrer, Peter Reiss, Ard van Sighem, T. Sonia Boender, Kholoud Porter, Richard Gilson, Dimitrios Paraskevis, Metallidis Simeon, Georgia Vourli, Santiago Moreno, Inmaculada Jarrin, Caroline Sabin; Statistical analysis: Sara Lodi; Roger Logan; Interpretation of the data: All authors; Drafting the article: Sara Lodi, Miguel Hernan; Reviewing of the article: All authors; Critical revision for important intellectual content: all authors; Final approval of the submitted version: all authors: All authors.

Abstract

Background. For people living with HIV, major guidelines in high-income countries recommend testing for transmitted drug resistance (TDR) to guide the choice of first-line antiretroviral therapy (ART). However, individuals who fail a first-line regimen can now be switched to one of several effective regimens. Therefore, the virological and clinical benefit of TDR testing needs to be evaluated.

Methods. We included individuals from the HIV-CAUSAL Collaboration who enrolled <6 months of HIV diagnosis between 2006 and 2015, were ART-naïve, and had measured CD4 count and HIV-RNA. Follow-up started at the date when all inclusion criteria were first met (baseline). We compared two strategies: (i) TDR testing within 3 months of baseline versus (ii) no TDR testing. We used inverse probability weighting to estimate the 5-year proportion and hazard ratios (HR) of virological suppression (confirmed HIV-RNA<50 copies/mL), and of AIDS or death under both strategies.

Results. Of 25,672 eligible individuals (82% males, 52% diagnosed in 2010 or later), 17,189 (67%) were tested for TDR within 3 months of baseline. Of these 6% had intermediate or high-level TDR to any antiretroviral drug. The estimated 5-year proportion virologically-suppressed was 77% under TDR testing and 74% under no TDR testing; HR 1.06 (95% CI: 1.03,1.19). The estimated 5-year risk of AIDS or death was 6% under both strategies; HR 1.03 (95% CI: 0.95,1.12).

Conclusions. TDR prevalence was low. While TDR testing improved virological response, we found no evidence that it reduced the incidence of AIDS or death in first 5 years after diagnosis.

Introduction

Transmitted drug resistance (TDR) occurs when an individual is infected with a strain of HIV that is resistant to a single antiretroviral, an entire drug class or multiple classes. The prevalence of TDR in ART-naïve individuals in high-income countries ranges between 7% and 14% [1-7]. Clinical practice guidelines recommend TDR testing—a genotypic test— in all individuals newly diagnosed with HIV before initiating antiretroviral treatment (ART) [8-11]. The expectation is that TDR test results will guide the choice of ART agents and reduce the risk of using a less effective regimen. Use of a drug to which the virus is resistant could be detrimental in the long-term as it prolongs the time to achieve virological suppression and increases the risk of developing resistance to active treatments [12-15].

While TDR testing was shown to be beneficial in the early 2000s [16], rapid changes in the landscape of HIV treatment require a re-evaluation of the value of TDR testing. Treatments containing agents with a high barrier to resistance, such as integrase inhibitors and boosted darunavir, as well as several other potent second and third-line ART options are now widely available in high income settings. These innovations imply that, while most individuals will achieve adequate virological suppression from their initial regimen, those who do not, will likely do so after switching to an alternative treatment.

Here, we used observational data to estimate the effectiveness of TDR testing, when used according to current guidelines, on virological and clinical outcomes up to 5 years after HIV diagnosis among individuals diagnosed with HIV in Europe and Canada between 2006 and 2015.

Methods

Study data

The HIV-CAUSAL Collaboration is a consortium of prospective HIV cohorts from Europe and the Americas. All cohorts record routinely collected data in clinical practice within settings with universal access to care. Data collected include patient characteristics (age, sex, geographical origin, and transmission category), use of ART (type of regimes and dates of start and stop), CD4 cell counts, and plasma HIV-RNA, AIDS-defining conditions, and death (cause(s) and date). Each cohort submits data in a standardized format (http://www.hicdep.org/) to the coordinating center. The analyses presented here are based on data pooled from 7 cohorts within the HIV-CAUSAL Collaboration that contributed data on genotypic drug resistance testing conducted as part of routine clinical care: AMACS (Greece), ATHENA (Netherlands), CoRIS (Spain), Swiss HIV Cohort Study (Switzerland), the South Alberta Cohort Study (Canada), UK CHIC/UK HIV Drug Resistance Database (United Kingdom), and UK Register of HIV Seroconverters (United Kingdom). The date of a TDR testing was the date the blood sample for the testing was drawn, rather than the date of sequencing.

We defined a TDR test as any genotypic drug resistance test conducted while the individual was ART-naïve. Predicted resistance was derived for all individuals using the Genotypic Resistance Interpretation Algorithm, version 7.0 (HIVdb Program, Stanford University, http://hivdb.stanford.edu). TDR was defined as predicted intermediate or high level resistance to any of the following antiretroviral drugs in use during the study period: atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir (protease inhibitors - PI); lamivudine, emtricitabine, abacavir, didanosine, tenofovir, stavudine, zidovudine (nucleoside reverse transcriptase inhibitors - NRTI); nevirapine, efavirenz, etravirine, rilpivirine (non-nucleoside reverse transcriptase inhibitors - NNRTI). Resistance to integrase inhibitors fusion inhibitors and CCR antagonists were not routinely measured in the participant cohorts. Resistance data on integrase inhibitors were collected in only one cohort and were rare even in this cohort [17].

The date of ART initiation was the date that a patient initiated HIV treatment including at least two nucleoside reverse transcriptase inhibitors plus one or more of the following: an integrase inhibitor, protease inhibitors, a non-nucleoside reverse transcriptase inhibitor, an entry inhibitor or a fusion inhibitor. Regimens consisting of abacavir or tenofovir with two or more additional nucleoside transcriptase inhibitors were also considered ART regimens, but they were rare in our population (<2%).

Eligibility criteria

The analyses were restricted to individuals who met the following eligibility criteria between January 1 2006 and December 31, 2015: age ≥18 years, CD4 cell count and HIV-RNA measurements within 3 months of each other while ART-naïve and less than 6 months since HIV diagnosis. We restricted the analysis to individuals enrolled in clinics within cohorts where at least 30% of patients had received a genotypic drug resistance test while naïve.

TDR testing strategies

We compared the following two strategies: i) TDR testing under current recommendations, defined as genotypic drug resistance testing within 3 months while ART-naïve, and ii) no TDR testing, defined as no genotypic drug resistance prior to receiving ART. The 3-month time window for testing (the 'grace period') corresponds to the period within which 90% of TDR testing took place in our data. Note that our analysis emulates a pragmatic trial to estimate the effectiveness of TDR testing in which decisions concerning ART initiation are left to the discretion of the treating physicians. For descriptive purposes, we compared the proportion of individuals who initiated ART under the two strategies.

Outcomes

We considered the following two outcomes: i) virological suppression, defined as the second of two consecutive HIV-RNA<50 copies/mL after initiating ART, and ii) a combined endpoint of an AIDS-defining condition [18] or death. Separately for each outcome, we computed the 5-year

cumulative incidence under each strategy, the difference in cumulative incidence, and the hazard ratio.

Follow-up

For each individual, follow-up started at baseline, defined as the earliest date that all eligibility criteria were met, and ended at the earliest of developing the outcome, 12 months after the most recent HIV-RNA or CD4 count measurement (censoring due to infrequent laboratory measurements), cohort-specific administrative end of follow-up (ranging from December 2013 to November 2015), date of pregnancy when known, or initiation of an antiretroviral therapy combination not defined as ART.

Statistical analyses

For each outcome, we estimated the hazard ratio of TDR testing vs no testing via a pooled logistic regression model with an indicator for TDR testing strategy, month of follow-up (restricted cubic splines with 4 knots), and the following covariates at baseline: cohort, sex, HIV acquisition group (heterosexual contact, homosexual or bisexual contact, injecting drug use, or other/unknown), geographical origin (Western countries, sub-Saharan Africa, other, unknown), age (<35, 35-50, >50 years), HIV-RNA (<4, 4-5, >5 log10 copies/mL), CD4 cell count strata (<100-199, 200-349, 350-499, ≥500 cells/mm^3), AIDS and calendar year (2006-2009, 2010-2015) at HIV diagnosis. In the model for the virological outcome, we considered death as a censoring event. We also fit pooled logistic regression models for each outcome like the one described above and added an interaction term between month and the indicator of TDR testing strategy. The model's predicted probabilities were then used to estimate the 5-year cumulative incidence under each strategy and the difference in these values.

TDR testing strategies are defined over a 3-month grace period. For individuals who were not tested for TDR in the baseline month TDR testing is a post-baseline variable [19]. Therefore, to avoid immortal time bias we replaced each individual without a TDR test in the baseline month by two identical clones [20-22]. The first clone was assigned to the TDR testing strategy and was censored upon deviation from that strategy, that is, at 3 months if the individual had not received a TDR test by that time, or earlier at the time of ART initiation, if the individual initiated ART before receiving a TDR test during the grace period. The second clone was assigned to the no TDR testing strategy and was censored upon deviation from that strategy, that is, when the individual received a TDR test. Examples of how cloning and artificial censoring occurred under each TDR testing strategy are presented in Appendix Figure 1.

To adjust for the potential selection bias induced by censoring, we weighted each clone at each time by the inverse of the probability of remaining uncensored [21]. To estimate the weights for censoring due to deviating from the assigned TDR testing strategy, we fit two separate pooled logistic regression models for ART initiation before TDR testing and for TDR testing while ART-naïve in the original dataset. Each model included the previously listed covariates plus the most recent CD4 cell count (restricted cubic splines with knots at 200, 350, 500 and 1000 cells/mm^3),

HIV-RNA category (<1000, 1000-10000, >100000 copies/mL), diagnosis of AIDS (when the outcome was virological suppression) and months since the last CD4 and last HIV-RNA measurements. Individuals who had TDR testing at baseline month were assigned a weight equal to 1. To estimate weights for censoring due to infrequent laboratory measurements, we used a pooled logistic regression model with the same covariates as in the models listed above on the original dataset. We stabilized and multiplied the two sets of weights [23, 24]. The mean of the weights was 1.02 (min 0.20, max 7.8). Estimates of the effect of TDR testing remained basically unchanged in analyses with weights truncated at the 99th percentile.

We used a nonparametric bootstrap procedure based on 500 samples to obtain percentile-based 95% confidence intervals (CIs). All analyses were conducted with SAS version 9.4.

Sensitivity analyses

We conducted several sensitivity analyses to examine the robustness of our findings. First, because the proportion of individuals tested for TDR varied by center and cohort, we restricted the analyses to i) the three cohorts with highest overall occurrence of TDR testing (UK CHIC/UK Drug Resistance Database, Swiss HIV Cohort Study and Southern Alberta Cohort) and ii) centers in each cohort where at least 50% of patients were tested for TDR. Second, because some TDR may revert relatively quickly after infection in the absence of therapy (e.g. 184V, and K65R) [25], false negative tests might occur for individuals who had been infected with HIV for many years. We, therefore, repeated the analyses on the subset of individuals with early HIV disease defined as having a CD4 count> 500 cells/mm^3 at baseline. Third, to account for changes over time of antiretroviral combinations, we repeated the analysis separately by calendar period (2006-2009 versus 2010-2015). Fourth, as some TDR tests might have been conducted retrospectively on previously collected blood samples, we reran the analyses excluding individuals who initiated an ART combination including a treatment to which they were resistant. Fifth, we restricted the analyses to homosexual or bisexual males, the group with the highest prevalence of TDR testing and TDR detection in our data. Sixth, ART initiation might be prioritized over TDR testing in individuals with more advanced HIV disease such as late presenters. We, therefore, rerun the analyses changing the definition of TDR testing by allowing genotypic tests occurring within two weeks after ART initiation. Because individuals with late diagnosis are at risk of early virological failure and possibly faster clinical progression we restricted the analyses to individuals with late HIV diagnosis defined as having a CD4<200 cells/mm^3 or AIDS at baseline and to individuals with advanced HIV disease, defined as having a CD4<200 cells/mm^3 or AIDS at baseline [26]. Finally, in the analyses where virological suppression was an outcome, death was treated as a competing risk rather than a censoring event.

Results

Of 25,672 eligible individuals, 82% were men, 44% were late HIV presenters, and 52% started follow-up in 2010 or later. Their median (interquartile range [IQR]) CD4 cell count, HIV-RNA and age at baseline were 390 [221, 570] cells/mm^3, 4.6 [4.0, 5.2] $\log_{10}$ copies/mL and 36 [29, 44] years, respectively (Table 1). A total of 16354 (64%) individuals initiated ART at a median [IQR] CD4 cell count of 276 [160, 383] cells/mm^3, Of these 9953 (61%) started with a NNRTI regime, 5384 (33%) with a boosted PI regime, 778 (5%) with an INSTI regime, 228 (1%) with an unboosted PI regime, and 11 (<1%) with a 3 NRTI regime.

TDR testing while ART-naïve occurred in 67% of individuals within 3 months of baseline (91% of them during the baseline month). Median [IQR] follow-up was 31 [14, 58] and 24 [11, 49] months for individuals with TDR testing and no TDR testing, respectively. Of 17,189 individuals with TDR testing, 5.8% had TDR to any antiretroviral drug, 1.2% to any PI, 3.7% to any NNRTI and 1.7% to any NRTI. The most commonly detected TDR to individual drugs were to nevirapine (3.5%), efavirenz (3.0%) and stavudine (1.3%). Of those with a detected TDR, 5% initiated ART with a combination containing a drug to which they were resistant. The proportion of individuals with a detected TDR varied by cohort but was similar across subgroups defined by late HIV presentation status, sex, age, calendar year, CD4 count and HIV-RNA at baseline (last column, Table 1). Detected TDR was less common among injecting drug users than in other HIV acquisition groups.

Figure 1 and Appendix Figure 2show the cumulative incidence curves under the two TDR testing strategies assuming no informative loss to follow-up. As shown in Table 2, the estimated 5-year risk (95% CI) of AIDS or death was 6.0% (5.6, 6.4) under TDR testing and 5.7% (5.1, 6.4) under no TDR testing; difference 0.30% (-0.30, 0.94); hazard ratio 1.03 (0.95, 1.12).

The estimated 5-year proportion (95% CI) who achieved virological suppression was 77.4% (76.6, 78.2) under TDR testing and 73.7% (72.0, 75.4) under no TDR testing; difference 3.7% (2.1, 5.3); hazard ratio 1.06 (1.03, 1.09). The estimated proportion (95% CI) of individuals who had ever initiated ART by 5 years of baseline was 87% (85, 88) under TDR testing and 87% (83, 90) under no TDR testing.

The results of the sensitivity analyses are presented in Table 3. The results did not materially change when the analyses were restricted to individuals from the three cohorts with the highest rate of TDR testing, to those who were enrolled in centers with more than 50% TDR testing, to individuals with late HIV diagnosis, or to homosexual or bisexual males; when excluding individuals who initiated ART with a combination containing a drug to which they were resistant; or when death was considered as a competing risk. The estimated hazard ratios of virological suppression for TDR testing versus no TDR testing were similar for individuals with baseline in the period 2005-2010 and 2011-2015.

Discussion

In individuals diagnosed with HIV in high-income countries, we estimated that current recommendations for TDR testing, compared with no TDR testing, increased the proportion achieving virological suppression by 5 years from diagnosis by 3.7% but with no effect on AIDS or death in this time frame.

One explanation for the lack of any short term clinical benefit is the low prevalence of TDR (approximately 6% in our population), which imposes a hard limit on the maximum gain that can be achieved by TDR testing. As TDR testing may be beneficial in populations with higher TDR prevalence, care should be taken with extrapolating our results to resource-limited settings because of the differences in the TDR prevalence, HIV subtypes, CD4 count distribution at HIV diagnosis, and treatment patterns. Also, there may be other benefits of TDR testing that our study could not quantify, including some decrease in HIV transmission because of a modest increase in virological suppression [27, 28], and the generation of genotypic information to describe the dynamics of local HIV transmission (through phylogenetic tree studies) and the changing patterns of drug resistance [29-34].

Previous studies have compared the virological response after ART initiation for individuals with and without a previously detected TDR [12-15]. However, this approach might lead to selection bias if TDR testing affects the likelihood of ART initiation or loss to follow-up. Unlike these studies, we estimated the effect of TDR testing rather than of having a detected TDR. Importantly, we quantified the risk of the virological and clinical outcomes since baseline, a proxy of entry into HIV care and thus of the recommended time for testing, rather than since ART initiation. In fact, our approach parallels the design and emulation of a pragmatic randomized trial of TDR testing in which individuals are randomly assigned to either TDR testing or no testing while not intervening on other aspects of their care. Another strength of our study is the large sample size of over 25,000 individuals and the setting in HIV clinics in Europe and Canada that are considered representative of routine clinical practice where TDR testing is part of routine clinical routine [35].

TDR testing is controversial in individuals who present for HIV care with advanced immunosuppression and are therefore in need of immediate initiation of effective treatment [36, 37]. While TDR testing might be beneficial to identify the optimal treatment combination in a population with high mortality, it might also cause delays in initiating treatment and most clinicians would not want to wait for the result of the resistance test before initiating ART [38]. Also, because of the availability of several effective second-line options, patients who do not respond have the opportunity to be switched to an effective drug and virological suppression may end up being delayed only by a few months. A large proportion of patients in our population (44%) presented late for HIV diagnosis. We found that the hazard ratios of both the clinical and virological outcomes in the subset of individuals with late HIV diagnosis or advanced HIV disease at baseline were similar to the one in the overall population. This supports current TDR testing recommendations that do not vary by HIV presentation status.

Current guidelines worldwide recommend ART initiation with integrase inhibitors[39-42]. Only a small proportion of patients (5%) in our study initiated treatment with integrase inhibitors, so we could not appropriately assess TDR for this drug class, which seems to be rare at this point [11, 17, 43]. In high-income countries it is common practice not to delay ART initiation until the results of the drug resistance test become available, which usually takes two weeks[10]. Instead, because resistance can emerge quickly in low resistance barrier containing drugs[11], when an NNRTI-based regimen is considered as first-line treatment, the results of the resistance test should be available before starting treatment.

Our study has several limitations. First, the validity of our estimates relies on the untestable assumption that all confounders were adequately adjusted for. We expect this assumption to approximately hold because we adjusted for the most important known predictors for TDR including risk group, gender and calendar year. Second, some TDR tests could have been done retrospectively on stored blood samples, possibly in response to virological failure in individuals believed to have good adherence, which might have introduced bias. However, this is unlikely to have affected our estimates, because only 5% of patients with a TDR test started with a combination containing an antiretroviral treatment they were resistant to. Third, five years might not be a long enough period to examine differences in clinical outcomes. Finally, although TDR testing was recommended in all countries of the study between 2006 and 2015[44-47], the large proportion of individuals who were not tested (33%) might reflect incomplete data. The robustness of our results to sensitivity analyses restricting to centers with more than 50% patients tested for TDR and to cohorts with high TDR testing uptake is reassuring

In conclusion, we found a low prevalence of TDR in high-income countries. While TDR testing seems to improve virological suppression after ART initiation, we found no evidence that it reduced the incidence of AIDS or death for up to 5 years after baseline. These results call for more evidence to establish which populations would benefit from selective TDR screening.

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Table 1. Baseline characteristics of 25,672 eligible individuals, HIV-CAUSAL Collaboration 2006-2015.

Table 2. Five-year estimated cumulative incidence (95% confidence interval [CI]) of virological and clinical outcomes under TDR testing and no TDR testing, HIV-CAUSAL Collaboration 2006-2015.

Table 3. Sensitivity analyses: Hazard ratios of virological and clinical outcomes for TDR testing vs. no TDR testing, HIV-CAUSAL Collaboration 2006-2015

Figure 1. Cumulative incidence of AIDS or death by TDR testing strategy, HIV-CAUSAL Collaboration 2006-2015.